Transplantation of wild-type mouse hematopoietic stem and progenitor cells ameliorates deficits in a mouse model of Friedreich's ataxia.

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Public Summary:
Friedreich's ataxia (FRDA) is a rare, inherited, degenerative neuromuscular disorder that initially impairs motor function, such as gait and coordination, but can lead to scoliosis, heart disease, vision loss, and diabetes. Cognitive function is not affected. The disease is progressively debilitating, and ultimately requires fulltime use of a wheelchair. Previous studies have shown that FRDA is caused by reduced expression of a mitochondrial protein called frataxin (FXN) due to a two mutated or abnormal copies of the FXN gene. In the current analysis, the investigators used a transgenic mouse model that expresses two mutant human FXN transgenes and exhibits the resulting progressive neurological degeneration and muscle weakness.In this study, the investigators transplanted wild-type HSPCs into an FRDA mouse model, reporting that the HSPCs engrafted and soon differentiated into macrophages in key regions of the mice's brain and spinal cord where they appeared to transfer wild-type FXN into deficient neurons and muscle cells. This treatment resulted in the full rescue of the neurologic, muscular and cardiac anomalies in the FRDA mice.

Scientific Abstract:
Friedreich's ataxia (FRDA) is an incurable autosomal recessive neurodegenerative disease caused by reduced expression of the mitochondrial protein frataxin due to an intronic GAA-repeat expansion in the FXN gene. We report the therapeutic efficacy of transplanting wild-type mouse hematopoietic stem and progenitor cells (HSPCs) into the YG8R mouse model of FRDA. In the HSPC-transplanted YG8R mice, development of muscle weakness and locomotor deficits was abrogated as was degeneration of large sensory neurons in the dorsal root ganglia (DRGs) and mitochondrial capacity was improved in brain, skeletal muscle, and heart. Transplanted HSPCs engrafted and then differentiated into microglia in the brain and spinal cord and into macrophages in the DRGs, heart, and muscle of YG8R FRDA mice. We observed the transfer of wild-type frataxin and Cox8 mitochondrial proteins from HSPC-derived microglia/macrophages to FRDA mouse neurons and muscle myocytes in vivo. Our results show the HSPC-mediated phenotypic rescue of FRDA in YG8R mice and suggest that this approach should be investigated further as a strategy for treating FRDA.